

# THE EFFECT OF IODINE ON HYPERTHYROIDISM IN MAN

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## *Introduction.*

WHILE it is generally recognized that there is an intimate relationship between the supply of iodine to the body and the histological structure of the thyroid gland, it is not so evident that, either as the direct outcome of this connexion, or possibly, to some extent at least, independently of this relationship, iodine may have a potent influence on the regulation of metabolic processes in the body. Of the close connexion between the thyroid gland and iodine, both from a chemical and structural point of view, there is overwhelming evidence. The hyperplasia of the thyroid glands of dogs and other animals could be cured by Marine (1) in the course of a few weeks by iodine. The glands reverted to the normal structure, the columnar cells surrounding the alveoli in the hyperplastic glands changing to a cubical or flat shape and the alveoli becoming round and regular in contour and filled with an eosin-staining colloid. Other observations by Marine and his co-workers (2) on the goitres found in brook trout in certain breeding-ponds in America, and the reversion of their hyperplastic thyroids to normal structure and size following the introduction into the water of sea-water fish (containing iodine) as food, or iodides themselves, were of a parallel nature.

It is of interest to note that true hyperplasia of the thyroid, whether associated with symptoms of hyperthyroidism or not, is always related to a diminished iodine content, and the degree of hyperplasia is generally greater as the iodine in the gland diminishes. In fact absence of iodine seems to be a controlling factor in the development of this type of change, but whether it can be inferred that there has never been an adequate supply of iodine or that conditions have arisen which have driven the store of iodine out of the gland and out of the body is not known.

In addition to the evidence of the relation between iodine and thyroid hyperplasia there is also evidence of the relation between iodine and the development of colloid goitre. As the result of the endeavours of different workers, particularly Marine (3) in America, to eliminate goitres from districts

where they are prevalent, it has been found that small doses of iodides given to children prevent the development of these changes in the thyroid, and that, after prolonged treatment, they may bring about in some cases a reversion to the normal size of thyroids already enlarged.

But while iodine influences the structure both of hyperplastic thyroids in animals and of colloid thyroids in men, it is not obvious that it also influences the metabolism. The glands in these cases, although abnormal in structure, are generally not associated with any obvious abnormality of bodily function, nor does their reversion to normal following the administration of iodine bring about, so far as is known, any great change in the metabolic processes.

When we try to extend these facts to the problem of hyperthyroidism, we find great difficulties both of a theoretical and practical nature. Two questions present themselves for consideration: (1) Is hyperplasia of the thyroid gland always associated with some degree of hyperthyroidism? and (2) Is the thyroid gland always hyperplastic in human hyperthyroidism, and if so, is this type of hyperplasia similar in all respects to that found in animals? As regards the first question it can be said that in animals there may certainly be great hyperplasia without any obvious symptoms of hyperthyroidism. Slight degrees of hyperplasia may sometimes be found in human thyroids taken from subjects in whom no signs of hyperthyroidism had been detected, and goitres removed from patients without toxic symptoms may show the histological characters of active hyperplasia. It would appear, however, that in man any large degree of hyperplasia is not common in the absence of symptoms of hyperthyroidism, and Plummer (4) has said that 'if hyperplasia of the thyroid is of sufficient degree or extends over a long enough period, exophthalmos is almost sure to develop'.

It is also difficult to give a definite answer to the second question, viz. Is hyperthyroidism always associated with thyroid hyperplasia? In most cases it is certainly associated with thyroid abnormality, and this abnormality is most commonly hyperplasia or includes hyperplasia. However, Marine (5) found in 137 cases of exophthalmic goitre, where the gland was examined at autopsy or after operation, there was some degree of active hyperplasia in 60 per cent. of the cases only and the symptom-complex was not associated with either constant or characteristic changes in the thyroid. All he admits is that the proportion of glands with active hyperplasia at the time of operation is higher in a series of exophthalmic goitre cases than in cases of simple goitre. This statement, which has as its corollary the view that hyperplasia of the thyroid is secondary in character and is not the primary cause of hyperthyroidism, has been endorsed by MacCallum (6) and rests on evidence confirmatory of the observations made originally by Virchow (7). Naturally the view has been opposed by others, more especially by surgeons, including C. H. Mayo (8), because of the obvious effect on the symptoms that follow operative interference with the thyroid in exophthalmic goitre.

While, therefore, it is difficult to give definite answers to the above questions, the experience of those who, like Marine, have had exceptionally great

opportunities for studying the problem, indicates that although thyroid hyperplasia plays some part and probably an important part in hyperthyroidism, it is not the sole and possibly not even the primary cause of the symptoms.

During the past few years we have been making observations in Sheffield on conditions which tend to the production of thyroid hyperplasia in dogs, in the hope of showing what factors might possibly determine the thyroid changes commonly found in exophthalmic goitre in man. In a preliminary communication some of these have been mentioned by E. and M. Mellanby. This work, though by no means complete, indicates in a general way that those dietetic and environmental conditions which bring about the most rapid bodily growth, absolutely or relatively to the size of the diet, favour the development of hyperplasia, while any condition which prevents increase in body-weight tends to the production of small glands more normal in structure. In all cases iodine in the diet keeps the glands small. Probably for this reason there is a great difference between the effect of cod-liver oil and butter. Cod-liver oil contains a small amount of iodine, and when present in the diet the thyroids remain small and normal. Butter, on the other hand, has a definite tendency to produce hyperplasia. More detailed publication of these facts will follow later, but we wish to state here that on the basis of this experimental work all the patients treated for hyperthyroidism have been given a diet which, while qualitatively sound, is of small energy value. Consideration of the action of the diet itself in hyperthyroidism we will hold over to a later occasion, but we may say here that there is evidence that it plays a part in the production of results described in this paper.

As regards the action of iodine in the diet the evidence of earlier workers discussed above shows that a supply of this substance both prevents the development of thyroid hyperplasia and converts a hyperplastic into a normal gland. It might, therefore, be expected that in cases of hyperthyroidism associated with thyroid hyperplasia the effect of iodine would be to cause the gland to become normal. Marine and Lenhart (9) say that this does happen and that in 15 cases of undoubted exophthalmic goitre iodine was rapidly stored by the gland and produced involution to the colloid state, and that, in fact, the thyroid hyperplasia of exophthalmic goitre behaved towards iodine exactly as did simple thyroid hyperplasia in animals. Now if this be true it seems to clinch the question as to whether or not thyroid hyperplasia is responsible for hyperthyroidism, for after a few weeks of iodine medication the hyperplasia should disappear and the symptoms of hyperthyroidism should clear up if they are related as cause and effect. This certainly does not happen. Either, then, iodine does not produce the same effect on the thyroid apparatus in cases of hyperthyroidism as in simple hyperplasia or the hyperplasia is not the primary part of the mechanism responsible for the symptoms of hyperthyroidism. Although we have not been able to formulate definite views on this and many other problems in this investigation, we may say that our inclination is to the belief that iodine does not have the same effect on thyroid hyperplasia associated with hyperthyroidism as it does on simple hyperplasia of the thyroid. We agree that there is a strong

tendency for the gland to revert to the normal under the influence of iodine, but there seems to be another active factor tending to withdraw iodine or iodine-containing compounds away from the gland and so preventing this reversion.

While it is generally agreed that iodine does influence exophthalmic goitre, there is no unanimity as to what the action is or what is its value in treatment. Kocher (10) taught that the administration of potassium iodide must never be carried out in exophthalmic goitre, and, on the whole, this advice has been taken. As evidence of this fact may be mentioned the discussion on the treatment of exophthalmic goitre at the Royal Society of Medicine in 1923. No speaker mentioned iodine or any preparation of iodine as being of any value in the treatment of the disease, and it can be inferred that therapy involving the use of iodine has been deliberately avoided. Recently Walton (11) has written that there is a very considerable danger in giving this drug if there is the slightest evidence of hyperthyroidism. Moreover, it has frequently been found that iodides given to goitrous patients without any toxic symptoms may provoke severe symptoms of hyperthyroidism.

Against these widely accepted experiences may be set the contrary observations of Neisser (12), who in 1920 reported that he had treated cases of Graves's disease with minute doses of sodium iodide and had obtained very striking clinical improvement. The work was repeated in 1921 by Loewy and Zondek (13), who found that there was a large fall in the oxygen consumption of his patients after the administration of small doses of iodides as used by Neisser, and that their weight began rapidly to increase at the same time. Since then favourable reports of this method of treatment have been published by Beebe (14) and others in America, and by Jagić and Spengler (15) in Vienna. The point to be noticed about these results is that much smaller doses of iodine were administered than is usual in iodine therapy. The difference in the results from those usually found was doubtless due to this fact.

Independently of Neisser's work E. and M. Mellanby reported to the Physiological Society and the Association of Physicians, in 1921, that they had been making some observations on the dietetic treatment of exophthalmic goitre. They gave patients suffering from this disease such food-stuffs free from iodine as had been found to produce in growing puppies the least hyperplastic thyroids—that is, food-stuffs which would be expected to make the smallest demands on thyroid activity and possibly, in consequence, be most compatible with the reversion to normal of hyperplastic glands. At the same time iodine was given either in the form of cod-liver oil or in small doses of potassium iodide. The iodine of cod-liver oil is present in minute quantities and its action becomes evident only after some time. The early effect of giving the oil to these patients is usually to increase the metabolism and the symptoms, and to cause a loss of weight. Under this treatment the subsequent improvement in many of the cases was striking, and a rapid gain in weight, and reduction in the intensity of the nervous symptoms and tachycardia, were observed. Further experience showed that the small doses of iodine played a prominent part in effecting the alleviation of

symptoms, but it became clear that the iodine effect was complicated and that its influence varied greatly according to such circumstances, among others, as size of dose, duration of treatment, and type of case. It was decided to make a closer study of its action, and work was directed to finding out how it acted and the conditions under which its best therapeutic effect could be obtained. The results of the investigation are described below.

It is clear that an investigation of this nature has a wider interest than that dependent on its immediate or even its ultimate clinical value. It has been seen above that iodine controls largely the structure of the thyroid gland, but that the evidence that it influences metabolic processes in the body, although such processes are greatly affected by thyroid activity, is small. This situation appeared enigmatical. However, the dramatic effect of iodides in hyperthyroidism makes it clear that thyroid function as well as structure may be greatly influenced by this substance, and that the physiological action of iodine cannot be explained simply by the fact that it forms part of the active principle thyroxin. We have had in our minds throughout this work the hope of shedding further light on this relationship between iodine and thyroid activity, as well as finding out the conditions under which the best clinical results can be produced in cases of hyperthyroidism.

#### *Methods.*

Patients suffering from various types of hyperthyroidism have been kept under observation in hospital, and records of their basal metabolic rate, pulse-rate, weight, neck measurement, and general clinical condition have been made at frequent intervals. The patients received during their stay in hospital a standard diet, the energy value of which was in the neighbourhood of 1,800 calories. It was usually arranged as follows:

Breakfast: 1 egg, 3 oz. bread with jam,  $\frac{1}{2}$  pint milk.

Lunch:  $\frac{1}{2}$  pint milk.

Dinner: 2 oz. lean meat, 4 oz. potatoes, 4 oz. green vegetables, small portion of milk pudding, 1 orange.

Tea: 3 oz. bread with jam, tea with a little milk.

Supper:  $\frac{1}{2}$  pint milk.

The basal metabolic rates were determined by the Douglas bag method and the pulse-rates recorded on the accompanying charts were taken while the patients were at rest under as nearly as possible basal conditions. It should be mentioned that the conditions for obtaining 'basal' measurements were not ideal; with one exception (Case I) the samples of air had to be collected in a general ward, although by the use of screens the disturbing effect of outside influences on the patients was to some extent avoided.

Iodine was given in the form of potassium iodide. The administration was begun at varying intervals after the patients' admission, in some cases after they had been resting in hospital for six weeks or two months. The largest amount

given was 18 grains in the day, the smallest 1 grain. The effects of temporarily discontinuing the iodide and of varying the dosage were observed in many of the patients.

A brief account of the history and clinical record of eight patients follows. To each case there is appended a chart on which are recorded graphically the B.M.R., pulse-rate, and weight taken at short intervals during the period of observation.

### Case Reports.

#### Case I. Moderately severe exophthalmic goitre.

*History.* M., a nurse, aged 35, had enjoyed good health till 1916. While nursing abroad she contracted malaria and was invalided home. She went abroad again in 1917 but did not feel really well, and towards the end of that year was again sent home. At this time she suffered from weakness, nervousness, and palpitations, and though she had no obvious enlargement of the neck she was informed that she had exophthalmic goitre. For the next

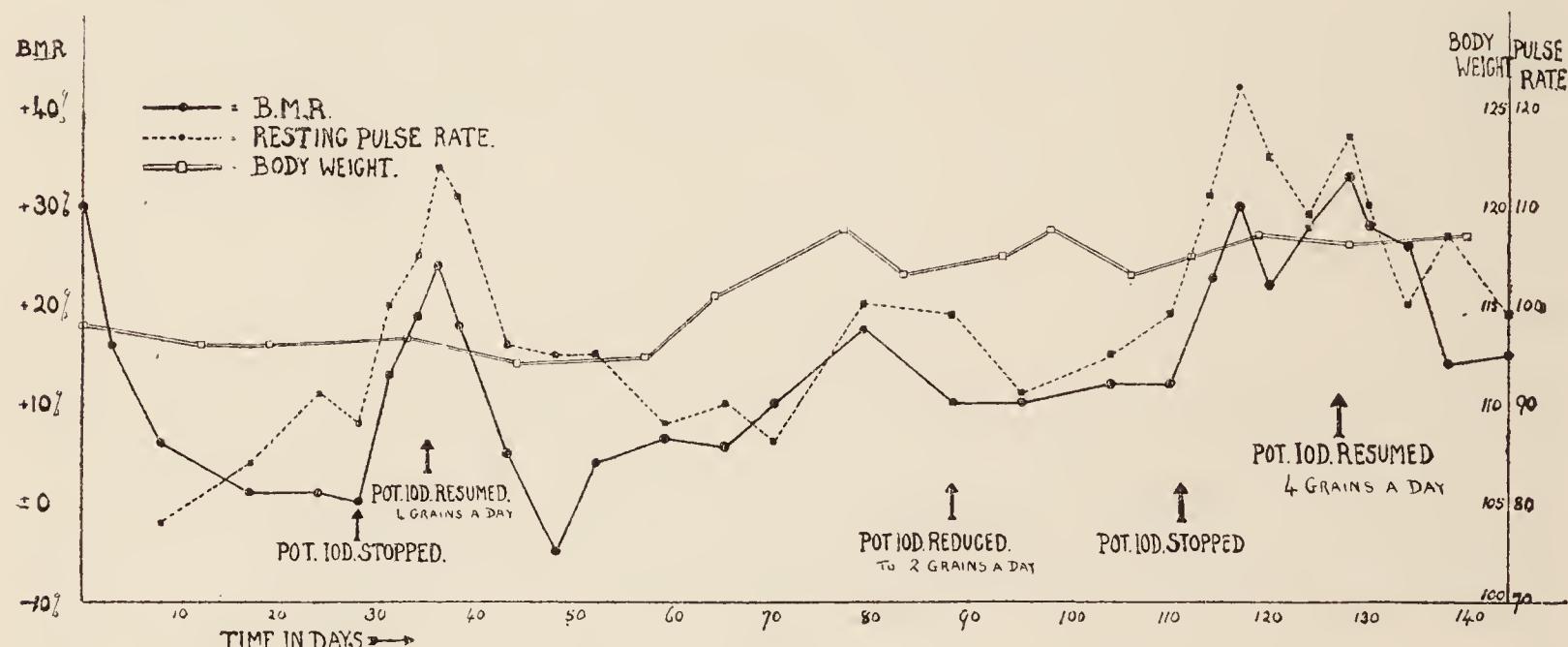


FIG. 1. Case I. Record of the B.M.R., pulse-rate, and weight. The effect of withholding iodide on two separate occasions is well shown.

three years she was able to do a little work occasionally. In 1920 her neck became obviously larger, and she was treated in hospital for six weeks with rest and X-rays. She gained considerably in weight, but remained weak and nervous. She was having a good deal of domestic worry at this time, and soon after leaving hospital became gradually worse, till towards the end of 1922 she got oedema of the legs and had to take to her bed. She was very depressed and irritable, and felt that life was a burden to her.

*Condition on admission.* Her chief complaints were of distressing palpitations and uncontrollable nervousness. She was moderately well nourished, had a slight but definite degree of exophthalmos and a moderate uniform enlargement of the thyroid. There was a fine tremor of the hands and pronounced general nervous hyperexcitability with frequent flushing and sweating of the skin. The heart was completely irregular in its action ; the presence of auricular fibrillation was confirmed by electro-cardiographic records.

*Treatment.* The low calorie diet was started at once and 2 gr. of potassium iodide were given twice a day. Strict confinement to bed was ordered until very definite signs of improvement were observed. On two occasions the potassium iodide was withdrawn, once for a period of a week and a second time for a period of 16 days.

*Progress.* Detailed records of her progress are available only from the third week of treatment onwards. The accompanying chart (Fig. 1) shows the fluctuations of the B. M. R., resting pulse-rate, and weight during a period of five months. The early B. M. R. measurements were low because she had been undergoing treatment for three weeks before they were begun. The heart stopped fibrillating after one month of the régime described above, and nine months later its rhythm was still regular. It is interesting to note that on the resumption of the normal rhythm the pulse-rate fell at once to below 80, from which level it rose gradually to between 90 and 100, where it remained throughout the greater part of the period of observation. With the cessation of the fibrillation the symptoms were greatly relieved ; the excessive nervousness disappeared to a large extent and the exophthalmos became less obvious, but there was no alteration in the size of her neck.

After four weeks of treatment the iodide was stopped. Within three days the B. M. R. and resting pulse-rate had risen appreciably, and at the same time the symptoms were aggravated : there was more restlessness and greater nervous excitability. At the end of a week the iodide was once more given. Three days later the pulse-rate and B. M. R. began to fall, and after ten days of iodide administration they had returned practically to their original level.

For the next two months iodide was given continuously and the B. M. R. remained fairly steady at about + 10 per cent. Reduction of the dose from four grains a day to two had no apparent effect on the patient. But when the iodide was now again discontinued altogether a distinct exaggeration of the symptoms, accompanied by a rise in the B. M. R., was again observed. After its withdrawal for 16 days iodide was again given. Ten days later the B. M. R. had fallen to approximately its former level, and an improvement in the general clinical condition was apparent.

This patient was seen four months after her discharge from hospital. She had been taking iodide continuously during this period. She was then in very fair health and had resumed her work. She had no exophthalmos and no tremor of her hands, and had gained 15 lb. in weight. There was a definite reduction in the size of her neck. The pulse was regular in rhythm, but varied from 100 to 110.

#### *Case II. Severe exophthalmic goitre.*

*History.* F. B., a single man of 25, enjoyed good health until 18 months before admission to hospital, when he began to feel worried and anxious for no particular reason, and to get attacks of nausea and vomiting. Two or three months later he noticed that his eyes were becoming prominent. He then began to suffer from frequent headaches and a 'trembling' of his limbs. His friends noticed that his mental condition was changing ; he was becoming restless, emotional, and difficult to manage.

*Condition on admission.* He was pale and poorly nourished. He had a definite exophthalmos which was by no means extreme, although his eyes were not more than half closed during sleep and consequently felt sore when he awoke in the morning. The thyroid was uniformly enlarged and pulsated freely, a thrill and continuous bruit being perceptible over it. The heart was enlarged, the pulse-rate 120 and regular in rhythm. There was a fine rhythmic tremor of the hands and coarse involuntary jerky movements of the whole limbs occurred from time to time. He was excitable, restless, and suspicious ; he slept badly, and would sometimes start up at night as though about to attack his neighbours in the ward.

*Treatment.* Five days after his admission he was given 2 gr. of potassium iodide twice a day. This dose was kept constant for five weeks, and during the following nine weeks was increased, first to 3 gr. twice a day, then to 6 gr. twice a day, and finally to 6 gr. three times a day. After this large dose had been given for a fortnight the iodide was discontinued altogether for 16 days, and was then resumed in doses of 2 gr. twice a day. The iodide was now given continuously

for a period of four months, and was then once more discontinued for a fortnight, after which it was resumed.

*Progress.* During the first month his B. M. R. fell steadily from + 70 per cent. to between + 20 per cent. and + 30 per cent., his clinical condition improving at the same time. The B. M. R. then rose suddenly to + 50 per cent., at which level it remained for a week, and then settled down to a fairly constant value of about

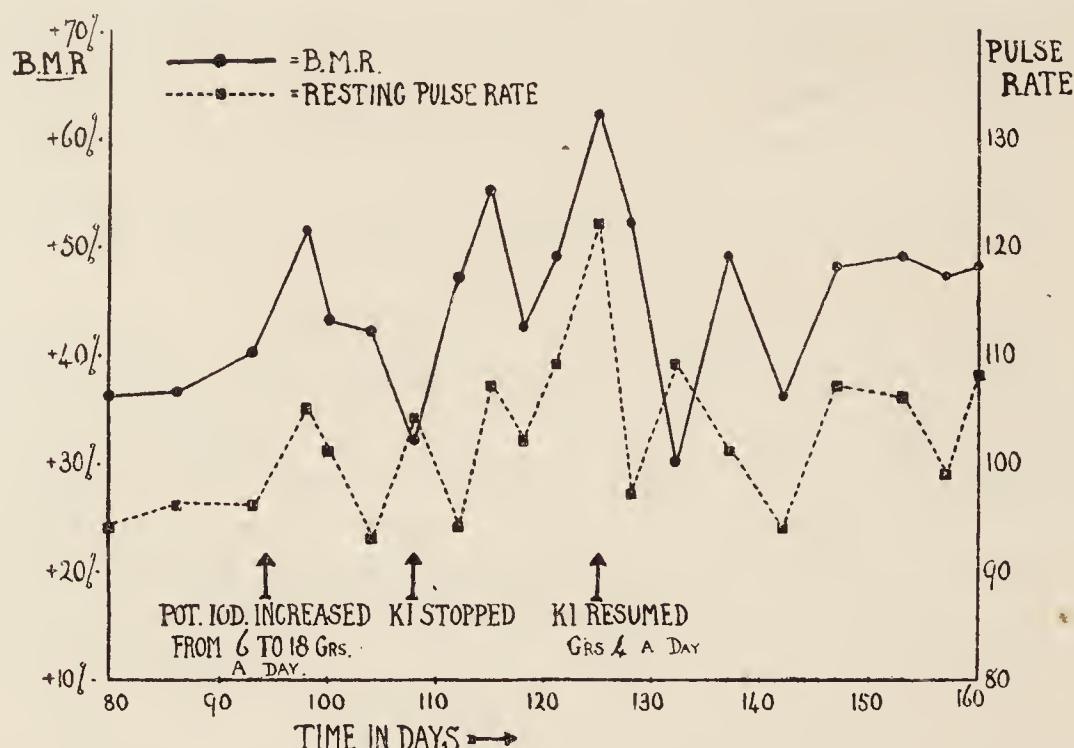


FIG. 2. Case II. The patient had been receiving large doses of iodide and showed severe symptoms at the beginning of the period illustrated here. The condition became worse, as is shown by a further rise in the B. M. R., when the iodide was stopped.

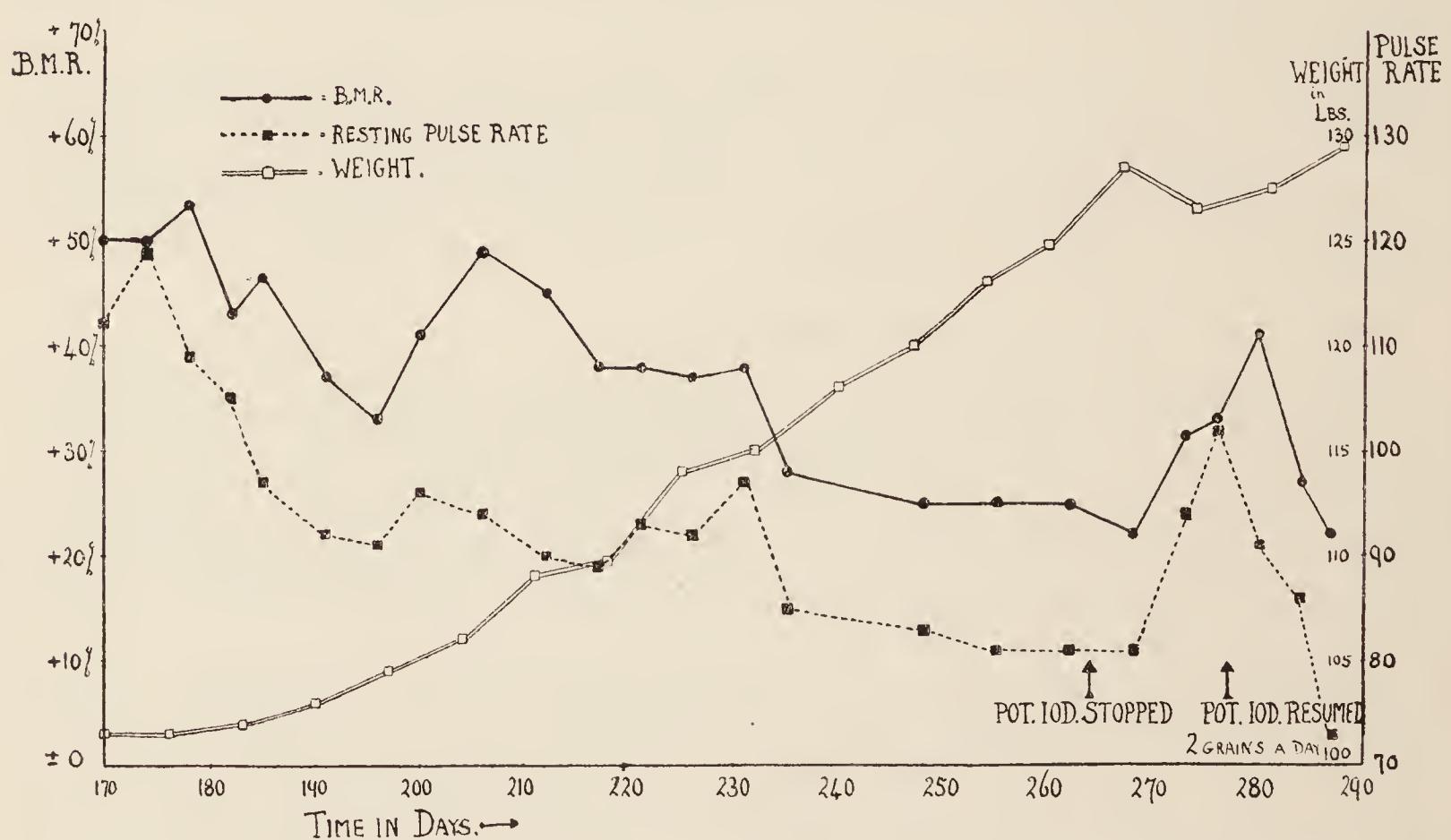


FIG. 3. Case II. A record of the same patient as Fig. 2, at a later period. During the greater part of this time he was receiving 1 gr. of iodide a day. The effect of stopping the iodide after its administration for nine months is seen.

+ 40 per cent., which was maintained for the next six weeks. During this period of six weeks the dose of iodide was increased on three occasions. The effect of raising the dose was on the last two occasions to cause an exaggeration of the nervous symptoms, which became apparent two or three days after the increased amount was given, but lasted only for a few days. This was particularly noticed when the large dose of 18 gr. a day was given: the symptoms became as severe, both subjectively and objectively, as they had been at the commencement

of treatment, and were accompanied by a transient rise of the B. M. R. After three or four days, however, he seemed to accommodate himself to the increased dose of iodide and the symptoms improved.

At this stage we decided to omit the iodide altogether. The result was a further exaggeration of the symptoms and a rise in the B. M. R. The iodide was withheld for 16 days and then recommenced in doses of 2 gr. twice a day. The resumption of the iodide was followed by an improvement in his condition and a transient lowering of the B. M. R., but the latter soon rose again and settled down to a constant level of about + 50 per cent., where it remained for the next month, being unaffected by a reduction of the iodide from 4 gr. a day to 2 gr.

He had now been in hospital for four months ; he was still very nervous and excitable, his pulse was rapid and his heart tumultuous in its action. His weight had at one time been slowly rising, but for the last month had been steadily falling. His goitre, however, was diminishing in size ; the neck measurement had been  $14\frac{1}{2}$  in. on admission and was now only  $13\frac{1}{8}$  in. A remarkable improvement now began to take place. The B. M. R. and pulse-rate fell steadily and the weight increased. This improvement was watched for three months, during the whole of which time he was receiving 2 gr. of iodide a day. At the end of this time his B. M. R. was + 25 per cent., his resting pulse-rate 80, and he had gained 27 lb. Iodide had been given altogether for 37 weeks and it was now stopped, medicine not containing iodide being substituted to eliminate any possible effect of suggestion. For the first few days there was no change in his condition ; then he began to complain of palpitations and disturbed sleep, and his pulse-rate and B. M. R. rose. His weight, which had been rising steadily for three months, began to fall. The iodide was withheld for 13 days and then resumed. Its resumption was very soon followed by a marked improvement in the symptoms and a rise in weight. Within 10 days the B. M. R. had fallen to + 20 per cent. and a resting pulse of normal frequency was observed for the first time.

### *Case III. Severe exophthalmic goitre.*

*History.* M. H., a single girl of 19, had 'always had rather a big neck', but took no notice of it till two years before admission to hospital, when it increased in size and she consulted her doctor about it. She felt quite well at this time and paid no further attention to the swelling of her neck till 18 months later, when she began to get short of breath and to suffer from frequent headaches. She then received a course of X-ray treatment which she states did not do her very much good. She had spent a month in bed shortly before coming into hospital, and had recently had a bout of vomiting which lasted a week.

*Condition on admission.* She was poorly nourished and very restless and excitable. She perspired freely and flushed deeply at the slightest provocation. She had pronounced exophthalmos with a well-marked von Graefe's sign. The thyroid was very considerably enlarged but was not pulsating : the swelling was uniform and of firm consistence. The heart's apex-beat was displaced somewhat to the left. The pulse-rate was 140, the rhythm was regular, and its wave was distinctly of the collapsing type. There was no rhythmic tremor of the hands, although coarse jerky movements were apparent in the arms when an attempt was made to hold them out steadily.

*Treatment.* 2 gr. of potassium iodide were given twice a day after she had been under observation for a week. This dose was continued for two months and then reduced to 1 gr. twice a day. Six weeks later the drug was stopped altogether, but was resumed after eight days and kept on till her discharge.

*Progress.* It will be seen from the chart (Fig. 4) that the B. M. R. and resting pulse-rate were very considerably raised during the 10 days immediately following her admission. They showed a sudden fall 8 days after the iodide was begun, the pulse-rate dropping from 120 to 90 and the B. M. R. from + 65 per cent.

to + 20 per cent. This low level was maintained for three or four weeks and was accompanied by a marked improvement in the nervous symptoms. After this period both the B. M. R. and pulse-rate began slowly to rise, the B. M. R. reaching a level of about + 30 per cent. During this time her weight was increasing fairly steadily and her general condition was good. After the iodide had been given for four months it was withdrawn completely. Within a week there was a very noticeable return of the nervous symptoms; the B. M. R. was raised to + 60 per cent. and the pulse-rate to 136, and her weight began to fall. The iodide was resumed when it had been withheld for eight days. Its resumption was soon followed by an improvement in the general condition and a fall in the B. M. R.

During the 20 weeks of her stay in hospital she gained 25 lb. in weight. Her exophthalmos diminished a great deal, but her neck measurement increased by one inch and the thyroid was harder than at the time of her admission.

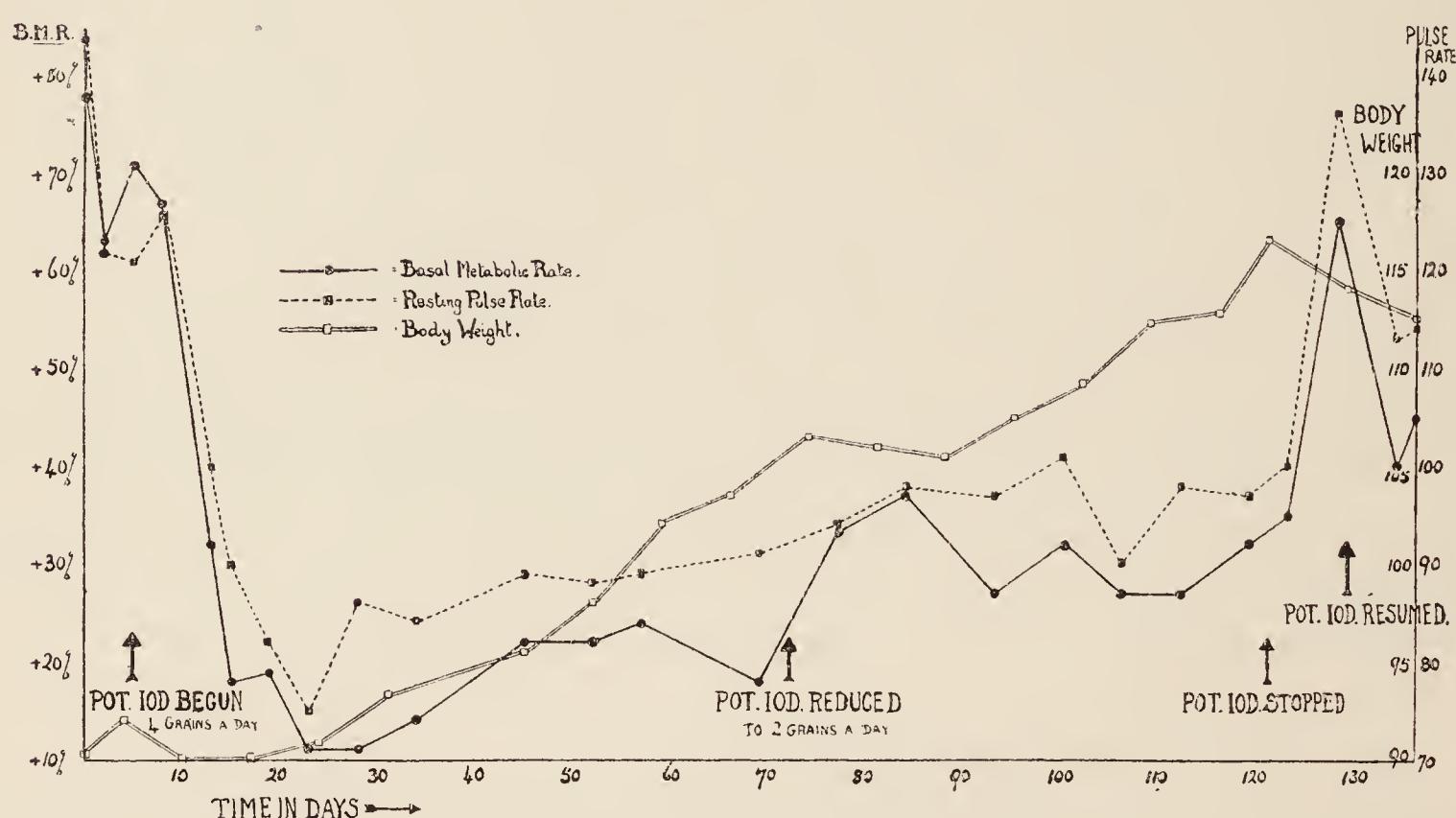


FIG. 4. Case III. The pronounced fall in the B. M. R. and pulse-rate during the first three or four weeks of the iodide administration is succeeded by a gradual rise. Withdrawal of the iodide after four months is quickly followed by a considerable rise in the B. M. R., accompanied by a fall in weight.

#### *Case IV. Moderately severe exophthalmic goitre.*

*History.* L. F., a married woman of 38, had enjoyed very good health until two years before coming under observation. At this time she was very much upset by the loss of one of her children and soon became thoroughly 'run down'. She got short of breath and felt tired out as soon as she started to do her work. She did not lose her appetite, but, in spite of eating more than she had been accustomed to eat, she lost a good deal of flesh. Some eighteen months after the onset of the symptoms she noticed that her neck was getting larger. Of late she had been getting worse and had had several bouts of vomiting lasting two or three days. She had not laid up in bed on account of her condition.

*Condition on admission.* She was poorly nourished, restless, and very excitable. She had a slight degree of exophthalmos, but no von Graefe's sign. The thyroid was uniformly enlarged to a moderate degree. The outstretched hands exhibited a fine tremor and the pulse-rate ranged between 100 and 120. The heart was regular in its action and did not seem to be enlarged.

*Treatment.* She was kept in bed for five weeks on the usual diet and given no other form of treatment. At the end of this period she was given two grains of potassium iodide a day, and this dose was continued for two weeks, when she left the hospital.

**Progress.** Two days after admission the B. M. R. was + 67 per cent. and the resting pulse-rate 125. Both the B. M. R. and pulse-rate fell steadily until at the end of three weeks the former was + 30 per cent. and the latter round about 90 (Fig. 5). At the same time there was a marked improvement in the symptoms, and the patient's weight, which had fallen very appreciably during the first week, began steadily to go up. During the next two or three weeks the B. M. R. remained in the neighbourhood of + 40 per cent., although the weight continued to rise and the pulse-rate to fall. Five days after the administration of potassium iodide had been begun the B. M. R. had fallen to + 17 per cent., and four days later was + 7 per cent., the resting pulse-rate being below 70. She was discharged from hospital after having taken the iodide for just over a fortnight. She had lost her tremor and her excessive nervousness, could take moderate exercise without feeling any shortness of breath or palpitations, and felt better than she had done for many months. There was no alteration in the size of her neck during her stay in hospital.

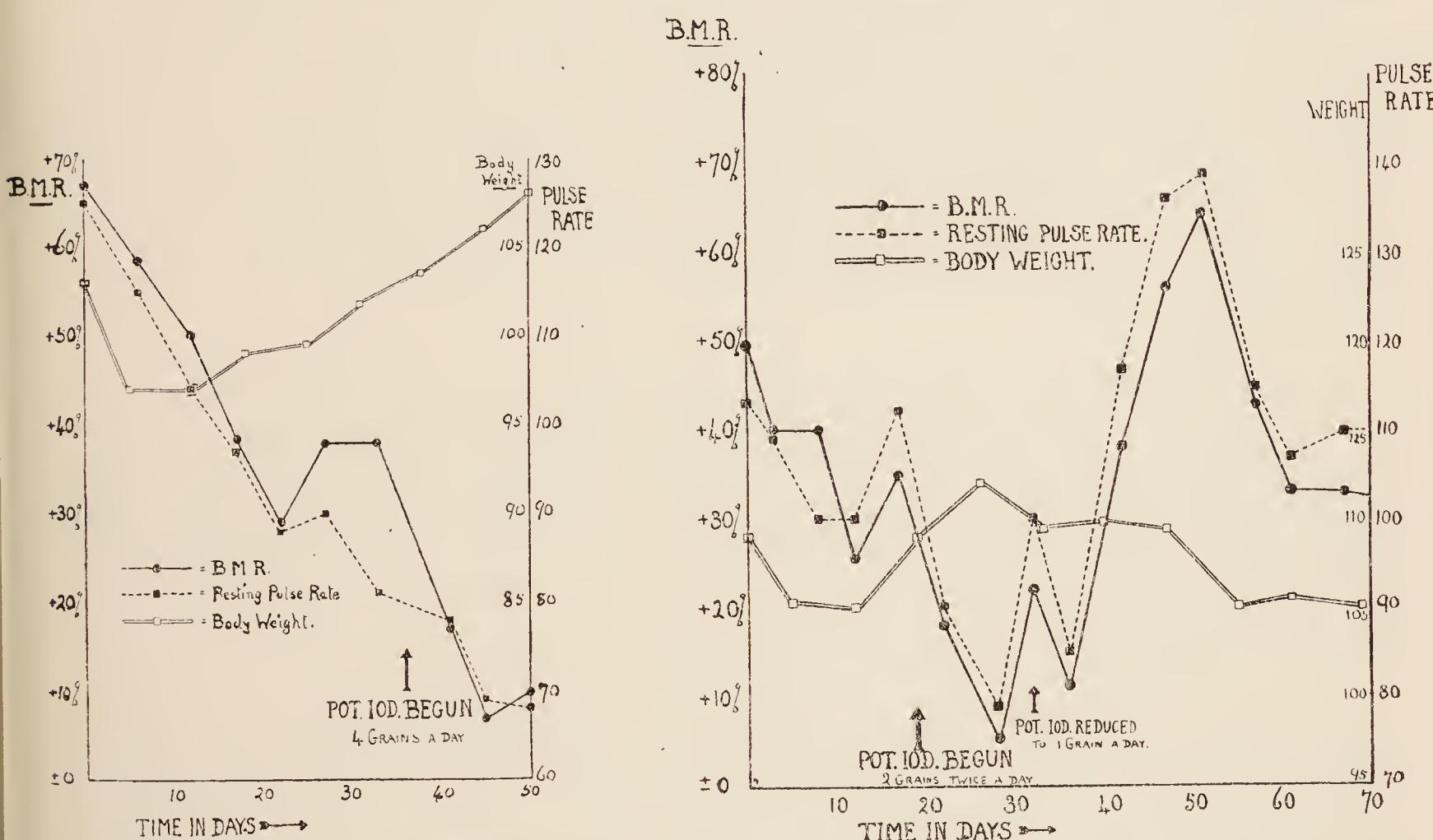


Fig. 5. Case IV. The patient had been resting in bed without medicine for five weeks before iodide was given. The B. M. R. fell considerably during this time, but a further rapid fall followed the giving of iodide.

#### Case V. Moderately severe exophthalmic goitre.

**History.** E. H., a married woman of 34, had been ailing for three years. She was troubled with frequent headaches and a constant sense of fatigue, and of late had been short of breath after slight exertion. She had noticed a swelling of her neck for a considerable time, but had not paid much attention to it. She had recently been receiving a course of arsenical injections, but her Wassermann reaction on admission to hospital was negative.

**Condition on admission.** She was moderately well nourished, had a slight degree of exophthalmos and a pronounced tremor of her hands. There was a diffuse enlargement of the thyroid, which felt soft and pulsated. Her heart was somewhat enlarged and her pulse-rate varied between 120 and 130. She exhibited a moderate degree of nervous hyperexcitability.

**Treatment.** She was kept at rest in bed for three weeks without medicine,

Fig. 6. Case V. The giving of iodide is followed by a considerable fall of the B. M. R. The low level is not maintained and is quickly succeeded by a rise to a higher point than it had ever reached before.

and then given two grains of potassium iodide twice a day for a fortnight. The iodide was then reduced to one grain a day.

*Progress.* During the first three weeks her B.M.R. varied between + 40 per cent. and + 25 per cent. (Fig. 6). She showed some signs of improvement towards the end of this period, but her pulse-rate had not fallen appreciably. Ten days after the commencement of the iodide there was a very marked general improvement. The B.M.R. had fallen almost to the normal level and the pulse-rate was below 80. She felt better than at any time during the past two years. This state of things did not last more than two or three days. Her thyroid then began to swell and became hard and tender. Pulsation in the gland had previously disappeared and now returned with greater intensity than before. The pulse-rate and B.M.R. quickly rose and her weight began to fall. At this point the iodide was reduced from four grains a day to one grain, but the reduction did not seem to influence the course of this 'reaction', which reached its maximum severity one month after the beginning of the iodide administration.

She now began to improve again, and the B.M.R. fell from the high level of + 65 per cent. which it had reached to the neighbourhood of + 30 per cent., where it remained for the next three weeks. During these three weeks the thyroid became softer and its pulsation disappeared, but it was not appreciably reduced in size. She left the hospital in much the same state as when she came in. She had lost two or three pounds in weight and was still excitable and had a rapid pulse. Her neck measurement had increased from  $13\frac{1}{2}$  inches to  $14\frac{1}{4}$  inches.

*Case VI.* Moderately severe hyperthyroidism without exophthalmos.

B.H., a single girl of 22, had noticed a swelling of her neck for nine years. She had felt perfectly well until she had an attack of scarlet fever eighteen months before admission to hospital. From this time onwards she found some difficulty in coping with her work, began to get severe headaches, and to suffer from shortness of breath and palpitations. Her work was very strenuous, but she had no particular cause for worry of any kind. She had a sister with a goitre, but this had never given any trouble and is said to have been 'cured'.

*Condition on admission.* She was well nourished, had a very considerable enlargement of her neck, but no suggestion of exophthalmos. She was excitable and suffered from vasomotor instability, as evidenced by frequent flushing and sweating of the skin. There was a fine rhythmic tremor of the hands and the pulse-rate varied from 120 to 150. There was a general enlargement of the thyroid and a small nodule could be felt in the left lobe; no pulsation could be felt in the gland. The heart appeared to be normal in size and was regular in its action.

*Treatment.* For five weeks she was kept in bed and given the fat-restricted diet; no other treatment was given during this period. Potassium iodide was then given in doses of two grains twice a day and continued for seven weeks until her discharge from hospital.

*Progress.* During the first ten days she was under observation, the B.M.R. fell from + 63 per cent. to + 23 per cent. and the pulse-rate from 120 to 90. She became less excitable and subjectively felt a distinct improvement, but was still troubled with frequent severe headaches. The B.M.R. then rose a little and for the next three weeks kept in the neighbourhood of + 30 per cent., while there was a corresponding rise in the resting pulse-rate. After the administration of potassium iodide had been started there was no immediate change in the clinical condition of the patient, although during the first week there was a distinct rise in the B.M.R. This preliminary rise was succeeded by a fall to a distinctly lower level than had been reached previously, and at the same time there was further improvement in the general symptoms, including the dis-

appearance of the headaches. The B. M. R. was on one occasion as low as + 5 per cent. (Fig. 7), but it fluctuated a good deal and at the patient's discharge was + 20 per cent. The resting pulse-rate varied during this time between 90 and 100. During her stay in hospital there was a noticeable alteration in the size of the thyroid. On admission the circumference of the neck measured  $14\frac{1}{4}$  inches; when the potassium iodide was begun it was 14 inches, and at the time of her discharge it was  $13\frac{1}{4}$  inches. The body-weight kept fairly steady during the whole period of observation.

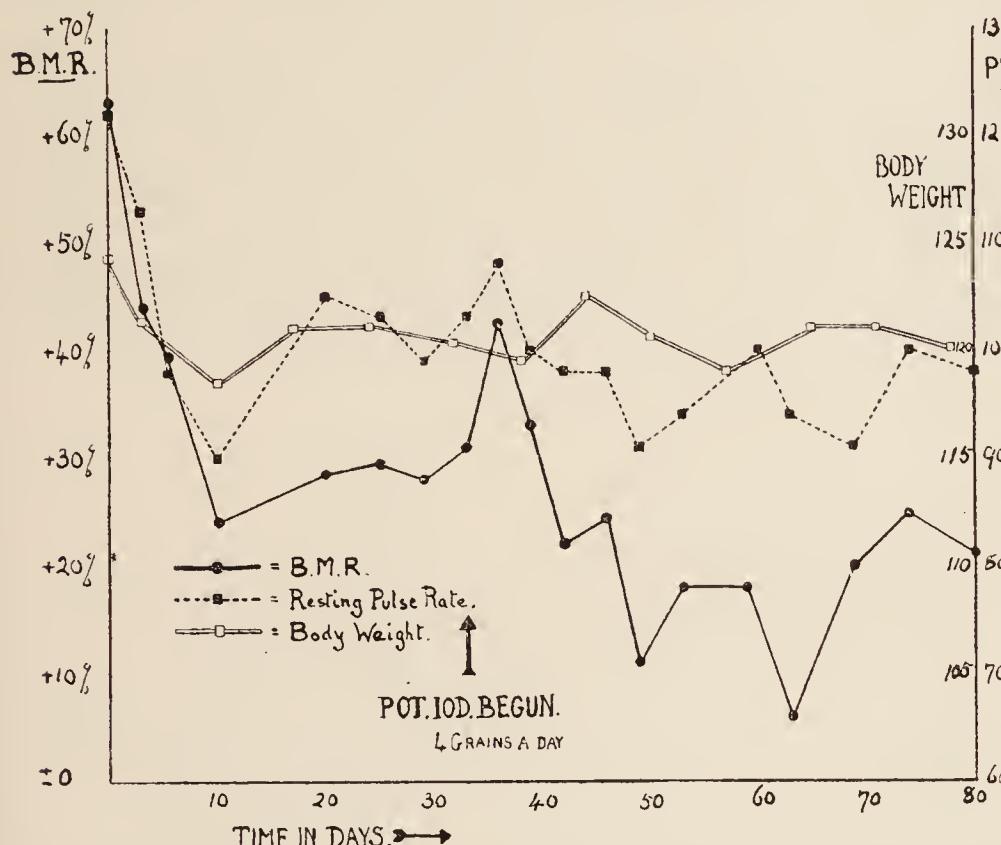


FIG. 7. Case VI. Iodide treatment was not begun till the patient had been resting for five weeks. It was followed by a definite fall in the B. M. R., although the pulse-rate was not greatly affected.

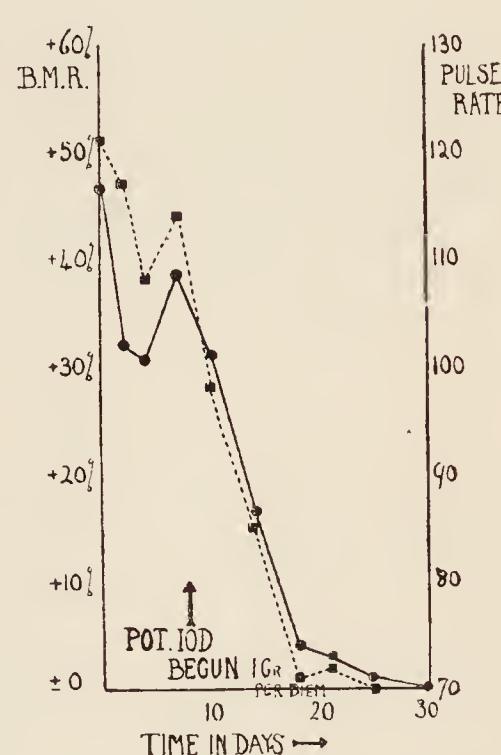


FIG. 8. Case 7. The B.M.R. reached the normal level ten days after the commencement of iodide administration. There is a very striking parallelism between the curves of the B. M. R. and pulse-rate.

#### Case VII. Mild hyperthyroidism without exophthalmos.

*History.* S. P., a clerk aged 32, complained of palpitations and nervousness which had troubled him for many years and which had become worse a few weeks before his coming into hospital. The palpitations were brought on more by excitement than by exertion, and were often accompanied by a tremor which temporarily prevented his continuing his work. He had been losing weight for the last year or two and had noticed a slight swelling of his neck.

*Condition on admission.* He appeared thin in the face, but was otherwise moderately well nourished. There was no definite exophthalmos, although the eyes were a trifle staring. There was a slight uniform enlargement of the thyroid, which showed no pulsation. The heart's apex beat was in the nipple line and the pulse-rate ranged from 110 to 120. There was occasionally a fine tremor of the hands.

*Treatment.* One-half of a grain of iodide was given twice a day, after eight days of observation, during which he was kept at rest in bed and fed on the special diet.

*Progress.* Before the iodide was begun the B. M. R. readings varied between + 30 per cent. and + 40 per cent. Five or six days after its administration there was an obvious improvement in the clinical condition and both the pulse-rate and the B. M. R. had fallen considerably. By the end of a fortnight the pulse-rate and B. M. R. had reached the normal level (Fig. 8) and the patient felt better than he had done for many years. The improved condition lasted

throughout the next three weeks, when an acute tonsillitis supervened. Two days after the subsidence of the fever the pulse-rate and B.M.R. were both somewhat raised, but at this stage he left the hospital, so that we were unable to determine whether the rise were a transient one due to the febrile attack or whether it represented the 'reaction' that has been observed in the majority of patients treated with iodides.

*Case VIII. Hyperthyroidism without goitre.*

*History.* A. W., a single girl of 21, was admitted to hospital with an acute pericarditis following pneumonia. She had some irregular pyrexia for three weeks, at the end of which time the pericarditis had apparently cleared up, leaving her emaciated, anaemic, and with a very rapid pulse. She was kept under observation for two months, during which she appeared to make no progress. She was extremely nervous and excitable, and her pulse was sometimes so rapid as to be almost uncountable. It was thought possible that her symptoms might be attributable to hyperthyroidism, and she was handed over to our care so that observations on this point might be made.

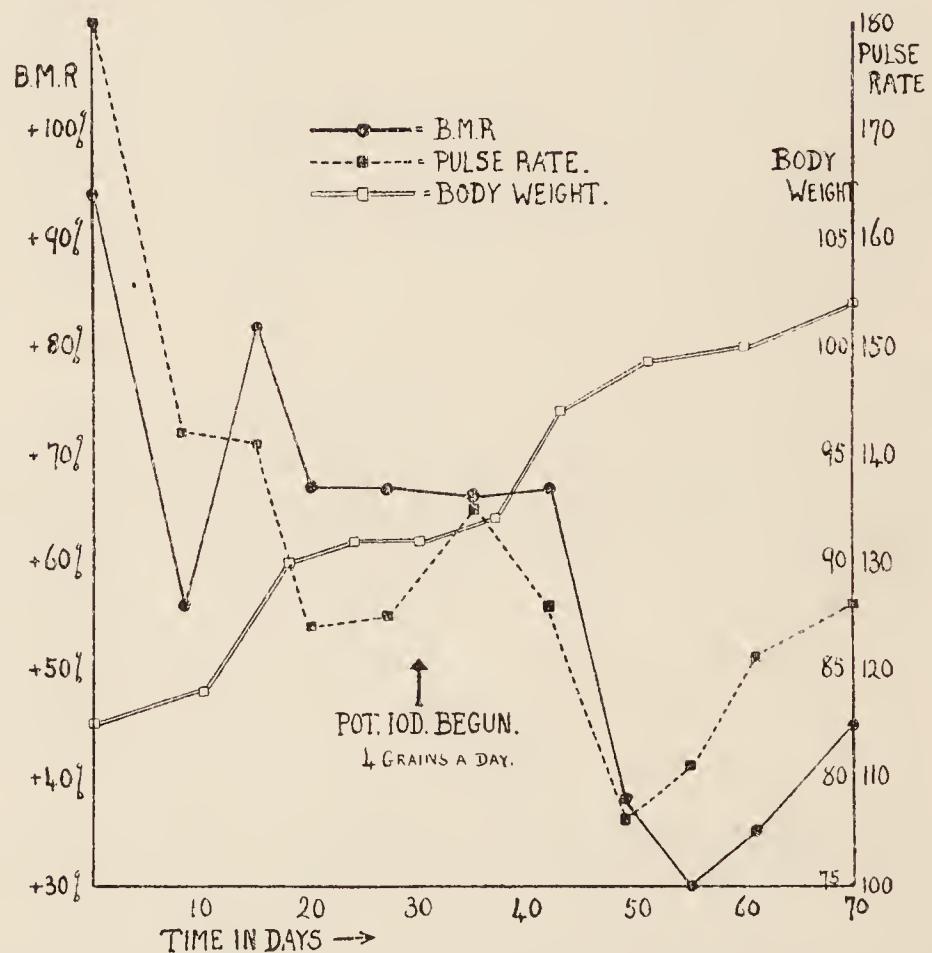


FIG. 9. Case VIII. It will be seen by examination of the weight-curve that this patient was improving during the four weeks preceding the iodide administration. There was a very considerable drop in the B.M.R. and pulse-rate between two and three weeks after the commencement of the iodide, but the comparatively low level reached at this stage was not well maintained.

*Condition at the time the present observations were begun.* She was pale and emaciated, weighing but 5 st. 12 lb. She was restless and excitable and had a well-marked tremor of her hands and lips. The heart was considerably enlarged, but there was no evidence of any valvular lesion. The thyroid was difficult to feel, and in fact seemed smaller than usual for a girl of her age. There was no suggestion of exophthalmos.

*Treatment.* She was kept on the diet for one month and was then given two grains of potassium iodide twice a day. This dose was kept up for the next six weeks until she left hospital. She was kept in bed at the beginning of the treatment, but as her general condition improved she was allowed to get up and take mild exercise.

*Progress.* She was so very excitable at first that it was found impossible to obtain consistent figures for her B.M.R. Thus during the first three weeks

she was under observation the measurements fluctuated between + 94 per cent. and + 56 per cent. After this she began to show definite signs of improvement, and although the B. M. R. kept steady at the high level of + 67 per cent., her weight slowly increased. The potassium iodide was started when the B. M. R. appeared to be more or less constant. There was no apparent effect on either the B. M. R. or pulse-rate for the first twelve days of its administration. There was then a fall in the B. M. R. of nearly 30 per cent., while the resting pulse-rate fell from 126 to 106. The fall in the B. M. R. was continued for a week, and a gradual rise then took place, so that on her discharge from hospital the B. M. R. was + 45 per cent. (Fig. 9).

During the ten weeks of treatment outlined above she gained 20 lb. in weight and lost much of her excessive nervousness. Her pulse-rate remained high, although she could take mild exercise without causing herself any distress. It is interesting to note that the circumference of her neck increased out of proportion to her general increase of flesh, and her thyroid could be very readily felt when she left hospital.

#### *Discussion of results.*

In every case of hyperthyroidism that we have observed up to the present time the giving of small doses of iodide has resulted in a distinct clinical improvement. This improvement becomes obvious at the end of a week, and as regards slowing of the pulse-rate, lowering of the B. M. R., and lessening of the general nervous excitability, attains a maximum between the tenth and the twentieth days of the treatment. From this time onwards we have observed considerable variation in the response of different patients. (1) They may remain for several weeks in this improved condition, with a low B. M. R. and slow resting pulse-rate, and then develop a slight and gradual return of the symptoms. (2) There may be a rather sudden return of the symptoms soon after their maximum decline, the patients continuing to put on weight and regain strength in spite of an increased metabolism and tachycardia. These two classes comprise the bulk of the patients that we have observed. (3) Occasionally there may be a more violent exacerbation in which the symptoms return within the course of a week or two to their original degree of severity. A striking example of this type of response was obtained in a patient whose case has not been detailed above. She had a large adenomatous thyroid of long standing with severe toxic symptoms. After four days of iodide treatment her B. M. R. fell from + 55 per cent. to + 8 per cent. with corresponding clinical improvement. The B. M. R. remained at this level for a fortnight and then rose quickly to its former level.

We are not able to predict with any certainty what course is likely to be followed by any particular case. It would appear, however, that those patients with large hard glands are more likely to develop severe 'reaction' symptoms than those with smaller soft ones.

The amount of iodide given does not appear, within certain limits, to control the rate of improvement noted in the early stages of treatment. Thus the giving of nine grains of potassium iodide a day has been followed by the same

rapid improvement that has been observed when one grain was given. We believe that when very small doses are given the return of symptoms tends to be longer delayed and less severe than when larger doses are given. We have not yet determined the minimum quantity of iodide that will exert a demonstrable effect, but it is less than half a grain a day. When a return of symptoms has occurred while the patient was receiving a comparatively small dose of iodide, no improvement has been found to follow the reduction of the dose; on the other hand, increasing the dose under these conditions has in our experience caused a still further exaggeration of the symptoms.

Withdrawal of the iodide has always been followed by an increase in the severity of the symptoms. Thus in Case II iodide had been given for nine months and the goitre had practically disappeared, yet when the iodide was stopped there was within a week a return of the tachycardia, an increase in the B. M. R., and a loss of weight. Resumption of the iodide has invariably been followed by a rapid return to the state that existed before the withdrawal.

We are unable to make any detailed statement concerning the effect of iodides on the structure of the thyroids in these cases, as we have obtained no material for histological study either from the post-mortem room or the operating theatre. Not uncommonly the glands become larger and firmer during the first few weeks of treatment. Pulsation in the glands diminishes in all cases and as a rule disappears after two or three weeks. In some cases there is subsequently a slow but steady diminution in the size of the goitre. During the more severe exacerbations the gland may increase in size and show signs of increased vascularity, but this change is not constant.

The aggravation of the symptoms that follows the withdrawal of the iodide even after many months of continuous administration lends some support to the suggestion mentioned in the introduction, that some factor may be at work which causes iodine to be withdrawn rapidly from the thyroid, thus allowing it again to become hyperplastic. It is possible that the presence of a certain quantity of iodine in the gland suppresses its activity to a maximum extent, but that the presence of more or less upsets the balance and allows an exaggeration of the symptoms to take place.

Examination of the figures shows that a considerable increase in weight is commonly observed while the patients are receiving iodide. This increase may occur while B. M. R. is as high as + 30 per cent. or even + 40 per cent., in spite of the comparatively low energy value of the diet.

After many months of treatment with small doses of iodide most of the patients retain to some degree their excessive nervous reaction to unwonted stimuli. This is seen particularly in those who have been discharged from hospital and attend as out-patients. They may present themselves with a rapid pulse and a tremor which they state they do not notice while they are engaged in their usual occupations.

In general it would appear that the mode of response of these patients to iodide therapy is remarkably similar to that observed to follow surgical treat-

ment. Similar periods of 'primary improvement' and 'relapse' described by Walton (16) as recognizable in all cases of exophthalmic goitre treated by surgical means have been illustrated in the above series of cases.

From the practical point of view we believe that the giving of small amounts of iodide to patients suffering from hyperthyroidism is a valuable adjunct to other medical treatment, and it is possible that doses of the order of  $\frac{1}{10}$  grain daily will prove to be the most suitable for the majority of cases. We have no grounds for considering this treatment as a curative one. It may prove useful as a preliminary measure in cases where surgical operation is considered advisable. Marine and Lenhart (9) found that in those cases which best withstood operative treatment the iodine content of the thyroids was higher than in the cases which showed severe post-operative disturbances, and put forward the view in 1911 that operations on these cases should not be undertaken until the thyroid had returned to its colloid state either spontaneously or by the action of minute doses of iodine.

From the standpoint of the physiology of the subject we are not yet in a position to discuss the bearing of these results on the part played by iodine in metabolism, apart from the fact that it is a constituent element of thyroxin. It seems certain, however, that iodine influences metabolic change in ways not at present understood.

#### *Summary.*

The relationship between the iodine content of the thyroid gland and the occurrence of the symptoms of hyperthyroidism in man is discussed. Small doses of iodides are shown to produce a lowering of the basal metabolic rate and distinct clinical improvement in patients suffering from hyperthyroidism. As regards the immediate results, this improvement reaches a maximum in from 10 to 20 days after the beginning of iodide administration, and is then frequently followed by a gradual return of the symptoms, which do not as a rule attain their former severity. The withdrawal of iodide from patients who have been receiving it continuously for several months is followed by an exacerbation of symptoms which can be relieved by once more administering iodide. Treatment by iodides of cases of hyperthyroidism of all types is recommended as an adjunct to other forms of medical treatment, and it is suggested that a course of iodide administration should prove of value as a preliminary to any surgical treatment of these cases that may be contemplated.

This investigation was carried out on behalf of the Medical Research Council, to whom our thanks are due.

## REFERENCES.

1. Marine, D., and Lenhart, C. H., *Arch. Int. Med.*, Chicago, 1909, iv. 253.
2. Marine, D., *Journ. Exp. Med.*, New York, 1914, xix. 376.
3. Marine, D., and Kimball, O. P., *Arch. Int. Med.*, Chicago, 1920, xxv. 661.
4. Plummer, H. S., *Journ. Amer. Med. Assoc.*, 1912, lix. 327-8.
5. Marine, D., *ibid.*, 1912, lix. 325.
6. MacCallum, W. G., *ibid.*, 1912, lix. 328; 1907, xlix. 1158.
7. Virchow, R., *Die krankhaften Geschwülste*, Berlin, 1863, iii, i. 74.
8. Mayo, C. H., *Journ. Amer. Med. Assoc.*, 1912, lix. 327.
9. Marine, D., and Lenhart, C. H., *Arch. Int. Med.*, Chicago, 1911, viii. 316.
10. Kocher, T., *Arch. f. klin. Chir.*, Berlin, 1910, xcii. 1166.
11. Walton, A. J., *Lancet*, Lond., 1923, ii. 58.
12. Neisser, E., *Berl. klin. Wochenschr.*, 1920, lviii. 461.
13. Loewy and Zondek, *Deutsch. med. Wochenschr.*, 1921, xlvi. 1387.
14. Beebe, S. P., *Med. Rec.*, New York, 1922, ci. 135.
15. Jagić, N., and Spengler, G., *Wien. klin. Wochenschr.*, 1923, xxxvi. 264.
16. Walton, A. J., *Lancet*, Lond., 1923, ii. 272.